PATENT ABSTRACTS OF JAPAN

(11)Publication number : 03-279325
(43)Date of publication of application : 10.12.1991

(51)Int.Cl. A61K 9/48

(21)Application number : 02-083676
(22)Date of filing : 29.03.1990

(71)Applicant : NIPPON ERANKO KK
(72)Inventor : YAMAMOTO TAIZO
ABE KENJI
MATSUURA SEINOSUKE

(54) RIGID CAPSULE FOR MEDICINE AND PRODUCTION THEREOF

(57)Abstract:
PURPOSE: To obtain the title capsule having low equilibrium water content in film and capable of preventing crack, deterioration, etc., due to water content after filling of chemical without causing brittleness even under low-temperature conditions.
CONSTITUTION: An aqueous solution of a base agent obtained by blending (A) a water soluble cellulose, preferably a cellulose ether (e.g. hydroxypropylmethyl cellulose substituted with an alkyl group and/or hydroxyalkyl group and used as a base with (B) a gelling agent, e.g. tamarind seeds, polysaccharides, pectin, gelatin, especially carrageenan and (C) a gelling assistant, e.g. potassium ion and/or ammonium ion in the case of carrageenan and containing 5-25wt.% of the ingredient A, 0.1-0.5wt.% of the ingredient B and 0.01-0.50wt.% of the ingredient C is prepared and a pin for forming capsule is dipped in the above- mentioned aqueous solution and the pin is pulled up and the aqueous solution of base attached to the outer surface is gelled to form capsule film.

LEGAL STATUS

[Date of request for examination]

[Date of sending the examiner's decision of rejection]

[Kind of final disposal of application other than the examiner's decision of rejection or application converted registration]

[Date of final disposal for application]

[Patent number]

[Date of registration]

[Number of appeal against examiner's decision of rejection]

[Date of requesting appeal against examiner's decision of rejection]

[Date of extinction of right]

(19)日本国特許庁（ＪＰ）　(12)特　許　公　報（Ｂ２）　(11)特許番号

第2552937号

(45)発行日　平成８年(1996)11月13日　(24)登録日　平成８年(1996)８月22日

(51)Int.Cl.[6]	識別記号	庁内整理番号	ＦＩ		技術表示箇所
Ａ６１Ｋ　9/48			Ａ６１Ｋ　9/48	Ｂ	
Ａ６１Ｊ　3/07			Ａ６１Ｊ　3/07	Ｄ	
Ａ６１Ｋ　47/38			Ａ６１Ｋ　47/38	Ｄ	

請求項の数６（全　４　頁）

(21)出願番号　特願平2－83676

(22)出願日　平成２年(1990)３月29日

(65)公開番号　特開平3－279325

(43)公開日　平成３年(1991)12月10日

(73)特許権者　999999999
日本エランコ株式会社
大阪府大阪市北区西天満６丁目１番２号
千代田ビル別館内

(72)発明者　山本　泰三
大阪府大阪市城東区関目１―20―30

(72)発明者　阿部　賢治
奈良県磯城郡三宅町屏風54―21

(72)発明者　松浦　誠之介
京都府相楽郡木津町兜台１－２－８－403

(74)代理人　弁理士　岩崎　光隆

審査官　後藤　圭次

(54)【発明の名称】　医薬用硬質カプセルおよびその製造方法

1

(57)【特許請求の範囲】

【請求項１】アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルを基剤とし、それにゲル化剤およびゲル化補助剤を配合してなる医薬用硬質カプセル。

【請求項２】アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルを５～25重量％、ゲル化剤を0.1～0.5重量％およびゲル化補助剤を0.01～0.50重量％配合するものである請求項（１）記載の医薬用硬質カプセル。

【請求項３】セルロースエーテルがヒドロキシプロピルメチルセルロースまたはヒドロキシプロピルセルロースである請求項（１）または（２）記載の医薬用硬質カプセル。

【請求項４】ゲル化剤がカラギーナンであり、ゲル化補

2

助剤がカリウムイオンおよび／またはアンモニウムイオンである請求項（１）、（２）または（３）記載の医薬用硬質カプセル。

【請求項５】アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテル、ゲル化剤およびゲル化補助剤を含むカプセル基剤水溶液を調製し、該基剤水溶液にカプセル成型用ピンを浸漬し、次いで該成型用ピンを基剤水溶液から引き上げて、当該成型用ピンの外表面に付着した該基剤水溶液を室温下にゲル化せしめ、前記成型用ピンの外表面にカプセル皮膜を形成せしめることを特徴とする医薬用硬質カプセルの製造方法。

【請求項６】カプセル基剤水溶液の液温を50～52℃とし、該基剤水溶液のゲル化を22.5～25.5℃の環境下に行うものである請求項（５）記載の医薬用硬質カプセルの

製造方法。

【発明の詳細な説明】

〔産業上の利用分野〕

本発明は新規な医薬用硬質カプセル、殊に基剤に公知のゼラチンを用いない低含有水分量の硬質カプセル、さらに詳しくは水溶性セルロース誘導体を基剤とした医薬用硬質カプセルとその製造方法に関するものである。

〔従来の技術〕

周知のとおり医薬用硬質カプセルは、通常ゼラチンを基剤とし、これにグリセリンまたはソルビトール等の可塑剤、さらに要すれば不透明化剤、染料または顔料等が適宜添加配合された皮膜組成物から成型される。そしてこのものは、該カプセル皮膜中に通常10～15重量％程度の水分を保有している。

もし、カプセル皮膜中の含有水分が10重量％以下になると皮膜の可塑性が失われ、当該カプセル内への薬剤の充填作業時における耐衝撃性が著しく損なわれて、使用に耐えなくなる。また、空あるいは薬剤充填後を問わず、該カプセルの保存時にも皮膜中の含有水分量が低下すると、該皮膜が収縮し、キャップとボデイの嵌合が経時的に緩くなるのを避け得ない。従って、かかる公知のゼラチン硬質カプセルでは、その皮膜中に前述のとおり一定の水分を保有せしめることが必須である。

ところが、このゼラチン硬質カプセルは、前記皮膜中の水分のために、内部に充填された薬剤が加水分解を受け易い場合、あるいは相互作用のある２種以上の薬剤が含まれているような場合には、分解して主薬の力価の低下、変質、変色、さらにはカプセル皮膜の不溶化等の不都合を惹起することがある。

こうした欠点を解消すべくこれまでにも医薬用硬質カプセルについて種々の改良、提案がなされている。例えば特公昭47－4310号公報には、セルロースの水酸基の一部もしくは全部がアルキル基あるいはヒドロキシ基で置換された水溶性セルロースエーテルを基剤として使用し、この水溶性浸漬液に成型ピンを浸漬し、皮膜を形成する硬質カプセルの製造法が開示されている。また、特開昭61－100519号および同62－266060号公報には、前記水溶性セルロースエーテルにポリビニールアルコール（PVA）を配合し、かかる水溶性浸漬液から硬質カプセルを得る方法について開示されている。

〔発明が解決しようとする課題〕

しかしながら、これらの医薬用カプセルは、水溶液セルロース誘導体の基剤浸漬液に成型用ピンを浸漬した後、成型用ピンまたは該ピンに付着した皮膜自体を加熱してゲル化成型せしめて製造されるので、その加熱が充分でないと前記基剤浸漬液がゲル化固化することなく、成型用ピンから浸漬液がずり落ちてしまい、実用上満足し得るカプセル皮膜を得ることができない。また、加熱温度が高すぎるとゲル化時の皮膜に皺が入り易い等の不都合を生じる。特に後者の場合、成型用ピンに付着した

水溶性セルロース誘導体を高温の水中で浸漬ゲル化させる際に僅かに成型物が水中に溶け出し、このため均一な皮膜を得ることが困難となるばかりでなく、このものはそのゼリー強度が小さいために、乾燥後成型用ピンから成型物すなわちカプセル皮膜の剥ぎ取りに際しても割れを発生することが多々あり、いずれにしても低含水量の医薬用硬質カプセルを実用的に得るのは困難である。さらに、これらのカプセル製造法を実施するには特別な装置と操作を必要とし、通常のゼラチン基剤からの浸漬成型なる最も一般的な公知のカプセル製造装置をそのまま利用することができない。

本発明は以上のような状況において案出されたものであり、上述の水溶性セルロース誘導体からなる硬質カプセルの難点、不都合を改善しようとするものであって、カプセル皮膜中の平衡水分が低く、低湿度条件下においても脆化せず、水分による薬剤充填後の割れ、変質等を防止せんとするものである。

〔課題を解決するための手段〕

本発明は、アルキル基およびヒドロキシアルキル基、もとはヒドロキシアルキル基で置換されたセルロースエーテルを基剤として、これにゲル化剤およびゲル化補助剤を添加、配合することにより室温下でのゲル化を可能としたものである。従って、本発明はアルキル基およびヒドロキシアルキル基、もとはヒドロキシアルキル基で置換されたセルロースエーテル、ゲル化剤およびゲル化補助剤を含む医薬用硬質カプセルとその製造方法をその要旨とするものである。

本発明において使用されるアルキル基およびヒドロキシアルキル基、もとはヒドロキシアルキル基で置換されたセルロースエーテルとしては、ヒドロキシプロピルメチルセルロースまたはヒドロキシプロピルセルロースを挙げることができるが、この中、ヒドロキシプロピルメチルセルロース皮膜成型性および低水分下での機械的強度の点において最適である。

一方、本発明において使用可能なゲル化剤としては、カラギーナン、タマリンド種子多糖、ペクチン、カードラン、ゼラチン、ファーセレラン、および寒天等を例示することができるが、カラギーナンはゲル強度が高く、しかも特定イオンとの共存下において優れたゲル化性を示すことから、少量の添加で使用可能となるので、特に好適なものである。なお、上記カラギーナンには、カッパカラギーナン、イオターカラギーナンおよびラムダカラギーナンの３種が知られているが、本発明においてはゲル化能を有するカッパおよびイオターカラギーナンを使用することができる。このゲル化剤カラギーナンのゲル化補助剤としては、カッパカラギーナンについてはカリウムイオン、アンモニウムイオンおよびカルシウムイオンの１種または２種以上を、またイオターカラギーナンについてはカルシウムイオンを挙げることができる。

ところで、本発明医薬用硬質カプセルの成型時（製

造）における浸漬液、すなわち、基剤水溶液の濃度は、アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルを５～25重量％、ゲル化剤を0.1～0.5重量％およびゲル化補助剤を0.01～0.50重量％の範囲でそれぞれ含有する。基剤水溶液中のアルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルの濃度が５重量％未満では、充分な厚みのカプセル皮膜を形成させることが困難であり、また、当該アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルの濃度が25重量％を越えると基剤のゼリー粘度が高くなり、浸漬法による均一なカプセル皮膜の成型が困難となる。従って、アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルの特に好ましい濃度は13～17重量％である。

一方、ゲル化剤としてのカラギーナンの濃度が0.1重量％未満では、浸漬成型時に成型ピンに付着した基剤水溶液がゲル化せずにピンからずり落ちてしまい、逆に0.5重量％を越えると前述の場合と同様に基剤のゼリー粘度が高くなり、浸漬法による均一なカプセル皮膜の成型が困難となるばかりでなく、浸漬液容器壁面にゲル化膜が発生し易くなり、カプセル皮膜成型時に支障を来す。従って、当該ゲル化剤の最適濃度としては、0.15～0.30重量％である。

さらに、前記ゲル化補助剤の濃度についても、前記範囲未満また範囲を越えての使用は、ゲル化剤の場合と同様の不都合を生じる。従って、かかるゲル化補助剤の最適濃度としては0.05～0.20重量％である。

本発明においては、公知の医薬用硬質カプセルと同様に前記基剤中には、必要に応じて色素、顔料等の着色剤、または不透明化剤、あるいは香料等を適宜配合することを妨げない。

本発明医薬用硬質カプセルは、公知のゼラチン硬質カプセルと同様に通常の浸漬成型法に準じて製造される。すなわち、アルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテル、ゲル化剤およびゲル化補助剤、さらに要すれば着色剤、不透明化剤、香料等を適宜配合して基剤水溶液を調整し、該水溶液に浸漬成型ピンを浸漬し、以下常法に従って硬質カプセル皮膜を得る。このとき該基剤水溶液、すなわち、浸漬液の温度は50～52℃に調整するのがよい。浸漬液の温度が前記範囲から外れると該浸漬液のゼリー粘度が微妙に変化し、浸漬成型時における成型ピンへの浸漬液の付着が良好に行われず、その結果均一なカプセル皮膜を得るのが困難となる。以後、浸漬液からの浸漬成型ピンの引き上げ、乾燥、成型ピンからの皮膜の剥ぎ取り（抜き取り）、および裁断等の工程を経て所定寸法の硬質カプセルが得られることは浸漬法による公知のゼラテン硬質カプセルの製造の場合と全く同じである。ただ、浸漬成型ピン外表面における基剤浸漬液のゲル化所要時間が、ゼラチン基剤の場合４～７秒であるのに対して本発明カプセルの場合では30～60秒とやや長時間を要する。

〔作用〕

本発明は上述したような特徴を有するので、特別な加熱を要することなく基剤のゲル化が達成され、低含水分量でも柔軟なカプセル皮膜を形成することができる。

〔実施例〕

以下実施例により本発明をさらに具体的に詳述する。

実施例１

約70℃の精製水19.55中に塩化カリウム18.4g（ゲル化補助剤濃度:0.08重量％）を加えて溶解し、さらにカッパカラギーナン39.1g（ゲル化剤濃度:0.17重量％）を加え、これらを撹拌しながら溶解する。

次に、この溶解液にヒドロキシプロピルメチルセルロース3.45kg（セルロース誘導体濃度:15重量％）を撹拌しながら投入し、温水中で分散させた後、該溶液温度を50℃に下げてヒドロキシプロピルメチルセルロースを撹拌しながら溶解し、その後７時間静置して脱泡する。

このようにして調整された浸漬液（基剤水溶液）を、浸漬法による公知のカプセル製造装置に仕込み、前記浸漬液の温度を50～52℃に保持しながら常法よりサイズ２号の硬質カプセルを得る。

試験－１（空カプセルの割れに対する評価）

前記実施例で得た本発明硬質カプセルと対照としてのゼラチン硬質カプセルについて、それぞれ12％RHの条件下で４日間放置し、皮膜中の含有水分を低下させた。また一方、同試料についてそれぞれ105℃で２時間乾燥し、皮膜中の含有水分を０％にした後、両試料カプセルを落錘試験法（49.7gの重りを20cmの高さから落下させる）と指圧試験法にて割れ状況を観察した。

その結果を第１表に示すが、本発明にかかる硬質カプセルはゼラチン硬質カプセルに比べて、明らかに割れにくいものであることが分かる。

第　１　表

カプセル	落錘試験		指圧試験	
	50個中の割れ個数	カプセル水分	10個中の割れ個数	カプセル水分
本発明品	0	1.1%	0	0%
対照品	46	8.8%	10	0%

試験－２（皮膜の平衡水分に対する評価）

実施例で得た本発明の硬質カプセルと前記対照カプセルについて、それぞれ43％RHの湿度、温度25℃の条件下に10日間放置し、平衡に達したことを確認した後、乾燥減量法でカプセル水分を測定し、皮膜の平衡水分を調べた。

その結果を第２表に示すが、本発明の硬質カプセルは

ゼラチン硬質カプセルに比べ、明らかに平衡水分が低く、低含有水分カプセルであることが分かる。

第　2　表

カプセル	平衡水分
本発明品	4.3%
対照品	13.9%

試験－３（空カプセルの溶状に対する評価）

実施例で得た本発明硬質カプセルと前記対照カプセルについて、日本薬局方規定の標準条件で、37±１℃に加温した精製水を用いた溶状試験を行った。

その結果を第３表に示すが、本発明の硬質カプセルは対照カプセルより溶状は遅くなるが、局方規定の10分以内に溶状が完了し、使用上支障を来すことはない。

第　3　表

カプセル	溶解時間	
	平均	最小～最大
本発明品	8′16″	7′27″～9′45″
対照品	3′53″	3′26″～4′45″

（供試カプセル数：5）

試験－４（崩壊性に対する評価）

実施例で得た本発明カプセルと前記対照カプセルについて、それぞれトウモロコシデンプンを充填し、日本薬局方規定の標準条件で、37±１℃に加温した第１液を用いた崩壊試験を行った。

結果は第４表－１および同－２に示すように本発明硬質カプセルは対照カプセルより崩壊はやや遅くなるが、３～５分以内で内容物の全てが完全に流出し、実用上充分に使用し得る硬質カプセル剤であることが確認された。

第　4　表　－　1

カプセル	カプセル開口時間	
	平均	最小～最大
本発明品	2′43″	1′47″～4′14″
対照品	1′02″	0′57″～1′08″

（供試カプセル数：6）

第　4　表　－　2

カプセル	内容物流出完了時間	
	平均	最小～最大
本発明品	3′45″	2′50″～4′55″
対照品	2′03″	1′58″～2′15″

（供試カプセル数：6）

〔発明の効果〕

本発明医薬用硬質カプセルは、上述のとおりアルキル基およびヒドロキシアルキル基、またはヒドロキシアルキル基で置換されたセルロースエーテルを主要基剤とするので、該セルロース誘導体により成型される皮膜の特性をそのまま硬質カプセルの特徴として享受するものである。すなわち、本発明によれば、

（１）低含水量の硬質カプセルを得ることができ、さらにその皮膜の機械的強度にも優れた医薬用硬質カプセルを提供することできる。

（２）皮膜中の平衡水分が低いので、水分により悪影響を受け易い薬剤に対してもそのまま当該硬質カプセル内に充填することができ、カプセル剤化が容易である。

（３）アルデヒド基またはカルボニル基との反応によりカプセル皮膜が不溶化することがない。

（４）基剤の副成分としてゲル化剤およびゲル化補助剤を用いるので、特別な装置および作業を要することなく、公知の浸漬法による硬質カプセル製造装置をそのまま援用して、安価に当該硬質カプセルを提供することができる。

* NOTICES *

CLAIMS

(57) [Claim(s)]

[Claim 1] A hard capsule for physic which makes a basis cellulose ether replaced by alkyl group and hydroxyalkyl radical, or hydroxyalkyl radical, and comes to blend a gelling agent and a gelation adjuvant with it.

[Claim 2] an alkyl group -- and -- hydroxyalkyl -- a radical -- or -- hydroxyalkyl -- a radical -- replacing -- having had -- cellulose ether -- five - 25 -- % of the weight -- a gelling agent -- 0.1 - 0.5 -- % of the weight -- and -- gelation -- an adjuvant -- 0.01 - 0.50 -- % of the weight -- blending -- a thing -- it is -- a claim -- (-- one --) -- a publication -- physic -- ** -- hard -- a capsule .

[Claim 3] A claim (1) whose cellulose ether is hydroxypropyl methylcellulose or hydroxypropylcellulose, or a hard capsule for physic given in (2).

[Claim 4] A claim (1) whose gelling agent is a carrageenan and whose gelation adjuvants are potassium ion and/or ammonium ion, (2), or a hard capsule for physic given in (3).

[Claim 5] Cellulose ether replaced by alkyl group and hydroxyalkyl radical, or hydroxyalkyl radical, Prepare a capsule basis aqueous solution containing a gelling agent and a gelation adjuvant, and a pin for capsule molding is immersed in this basis aqueous solution. Subsequently, a manufacture method of a hard capsule for physic characterized by pulling up this pin for molding from a basis aqueous solution, making this basis aqueous solution adhering to an outside surface of the pin for molding concerned gel under a room temperature, and making a capsule coat form in an outside surface of said pin for molding.

[Claim 6] a capsule -- a basis -- an aqueous solution -- solution temperature -- 50 - 52 -- degree C -- ** -- carrying out -- this -- a basis -- an aqueous solution -- gelation -- 22.5 - 25.5 -- degree C -- environment -- the bottom -- carrying out -- a thing -- it is -- a claim -- (-- five --) -- a publication -- physic -- ** -- hard -- a capsule -- manufacture -- a method .

[Translation done.]

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[Industrial Application]
This invention relates to the new hard capsule for physic, the hard capsule of the low content moisture content which does not use gelatin especially well-known to a basis, the hard capsule for physic that made the water-soluble cellulosic the basis in more detail, and its manufacture method.
[Description of the Prior Art]
As everyone knows, the hard capsule for physic usually makes gelatin a basis, and is cast by this from plasticizers, such as a glycerol or a sorbitol, and the coat constituent with which addition combination of opaquer, a color, or the pigment was suitably carried out when requiring further. And this thing usually holds about 10 - 15% of the weight of moisture in this capsule coat.
If the content moisture in a capsule coat becomes 10 or less % of the weight, the plasticity of a coat will be lost, the shock resistance at the time of restoration of the drugs into the capsule concerned is spoiled remarkably, and it stops being equal to use. Moreover, if the empty or drugs restoration back is not asked but the content moisture content in a coat falls also at the time of conservation of this capsule, this coat contracts and it cannot avoid that fitting of a cap and the body becomes loose with time. Therefore, it is indispensable to make fixed moisture hold in the coat by the well-known gelatin hard capsule to apply as above-mentioned.
However, it decomposes and this gelatin hard capsule has caused [the fall of the potency of a chief remedy, deterioration, discoloration, and] un-arranging, such as insolubilization of a capsule coat, further, when the drugs with which the interior was filled up for the moisture in said coat tend to receive hydrolysis, or when two or more sorts of drugs with an interaction are contained.
Various amelioration and a proposal are made about the hard capsule for physic until now that such a defect should be canceled. For example, the water-soluble cellulose ether with which some or all of a hydroxyl group of a cellulose was replaced by the alkyl group or the hydroxy group is used as a basis, a molding pin is immersed in this water-soluble immersion fluid, and the manufacturing method of the hard capsule which forms a coat is indicated by JP,47-4310,B. Moreover, poly vinyl alcohol (PVA) is blended with said water-soluble cellulose ether, and it is indicated by JP,61-100519,A and the 62-266060 official report about the method of obtaining a hard capsule from this water-soluble immersion fluid.
[Problem(s) to be Solved by the Invention]
However, without said basis immersion fluid carrying out gelation solidification, if the heating is not enough since the coat adhering to the pin for molding or this pin itself is heated, gelation molding is carried out and it is manufactured, after the pin for molding is immersed in the basis immersion fluid of an aqueous solution cellulosic, immersion fluid slips down and these capsules for physic cannot obtain the capsule coat which may be satisfied practically from the pin for molding. Moreover, if heating temperature is too high, it will produce un-arranging -- a wrinkle tends to go into the coat at the time of gelation. Especially in the case of the latter, in case immersion gelation of the water-soluble cellulosic adhering to the pin for molding is carried out by underwater [hot], molding begins to melt underwater slightly, and it

is [this] a sake. It is difficult it not only to become difficult to obtain a uniform coat, but for there to be a thing of molding, i.e., a capsule coat, for which a crack is generated plentifully from the pin for desiccation backward molding, even if it faces stripping off, and to obtain the hard capsule for physic of low moisture content practical anyway, since that jelly strength of this thing is small. furthermore, equipment and actuation special to enforcing these capsule manufacturing methods -- needing -- the immersion from the usual gelatin basis -- molding -- the most general well-known capsule manufacturing installation cannot be used as it is.
It is thought out in the above conditions and is going to improve the difficulty of the hard capsule which consists of a water-soluble above-mentioned cellulosic, and un-arranging, and the equilibrium moisture in a capsule coat is low, and does not embrittle under a low humidity condition, but this invention uses the crack after the drugs restoration by moisture, deterioration, etc. as a prevention plug.
[The means for solving a technical problem]
Gelation under a room temperature is enabled by adding and blending a gelling agent and a gelation adjuvant with this by making into a basis the cellulose ether with which this invention was replaced by the alkyl group and the hydroxyalkyl radical, and the basis was replaced by the hydroxyalkyl radical. Therefore, let the hard capsule for physic containing the cellulose ether, gelling agent, and gelation adjuvant by which this invention was replaced by the alkyl group and the hydroxyalkyl radical, and the basis was replaced by the hydroxyalkyl radical, and its manufacture method be the summary.
As cellulose ether replaced by the hydroxyalkyl radical, although the alkyl group used in this invention and a hydroxyalkyl radical, and a basis can mention the hydroxypropyl methylcellulose or hydroxypropylcellulose, they are the optimal in this in the point of the mechanical strength under a hydroxypropyl-methylcellulose coat moldability and low-water-flow part.
On the other hand, although a carrageenan, a tamarind seed polysaccharide, pectin, curdlan, gelatin, a furcellaran, an agar, etc. can be illustrated as an usable gelling agent in this invention, since it becomes usable by addition with a carrageenan little from the gelation nature which whose gel strength was high and was moreover excellent under coexistence with specific ion being shown, it is especially suitable. In addition, although three sorts, a kappa carrageenan, an IOTA carrageenan, and a lambda carrageenan, are known by the above-mentioned carrageenan, the kappa and IOTA carrageenan which have gelation ability in this invention can be used for it. As a gelation adjuvant of this gelling agent carrageenan, about a kappa carrageenan, one sort of potassium ion, ammonium ion, and calcium ion or two sorts or more can be mentioned, and calcium ion can be mentioned about an IOTA carrageenan.
By the way, the concentration of the immersion fluid at the time of molding of the hard capsule for this invention physic (manufacture), i.e., a basis aqueous solution, contains the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical, and contains 0.1 - 0.5 % of the weight, and a gelation adjuvant for a gelling agent in 0.01 - 0.50% of the weight of the range five to 25% of the weight, respectively. At less than 5 % of the weight, if it is difficult to make the capsule coat of sufficient thickness form and the concentration of the cellulose ether replaced by the alkyl group concerned and the hydroxyalkyl radical, or the hydroxyalkyl radical exceeds 25 % of the weight, the jelly viscosity of a basis will become high and it will become difficult to cast [of the uniform capsule coat by dip coating] the concentration of the cellulose ether replaced by the alkyl group and hydroxyalkyl radical, or hydroxyalkyl radical in a basis aqueous solution. Therefore, especially the desirable concentration of the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical is 13 - 17 % of the weight.
If it slips down from a pin, without on the other hand the basis aqueous solution with which the concentration of the carrageenan as a gelling agent adhered to the molding pin at less than 0.1 % of the weight at the time of immersion molding gelling and 0.5 % of the weight is exceeded conversely, it will become easy to generate a gelation film in an immersion fluid vessel-wall side, and like the above-mentioned case, the jelly viscosity of a basis becomes high and molding of the uniform capsule coat by dip coating not only becomes difficult, but will

is [this] a sake. It is difficult it not only to become difficult to obtain a uniform coat, but for there to be a thing of molding, i.e., a capsule coat, for which a crack is generated plentifully from the pin for desiccation backward molding, even if it faces stripping off, and to obtain the hard capsule for physic of low moisture content practical anyway, since that jelly strength of this thing is small. furthermore, equipment and actuation special to enforcing these capsule manufacturing methods -- needing -- the immersion from the usual gelatin basis -- molding -- the most general well-known capsule manufacturing installation cannot be used as it is.
It is thought out in the above conditions and is going to improve the difficulty of the hard capsule which consists of a water-soluble above-mentioned cellulosic, and un-arranging, and the equilibrium moisture in a capsule coat is low, and does not embrittle under a low humidity condition, but this invention uses the crack after the drugs restoration by moisture, deterioration, etc. as a prevention plug.
[The means for solving a technical problem]
Gelation under a room temperature is enabled by adding and blending a gelling agent and a gelation adjuvant with this by making into a basis the cellulose ether with which this invention was replaced by the alkyl group and the hydroxyalkyl radical, and the basis was replaced by the hydroxyalkyl radical. Therefore, let the hard capsule for physic containing the cellulose ether, gelling agent, and gelation adjuvant by which this invention was replaced by the alkyl group and the hydroxyalkyl radical, and the basis was replaced by the hydroxyalkyl radical, and its manufacture method be the summary.
As cellulose ether replaced by the hydroxyalkyl radical, although the alkyl group used in this invention and a hydroxyalkyl radical, and a basis can mention the hydroxypropyl methylcellulose or hydroxypropylcellulose, they are the optimal in this in the point of the mechanical strength under a hydroxypropyl-methylcellulose coat moldability and low-water-flow part.
On the other hand, although a carrageenan, a tamarind seed polysaccharide, pectin, curdlan, gelatin, a furcellaran, an agar, etc. can be illustrated as an usable gelling agent in this invention, since it becomes usable by addition with a carrageenan little from the gelation nature which whose gel strength was high and was moreover excellent under coexistence with specific ion being shown, it is especially suitable. In addition, although three sorts, a kappa carrageenan, an IOTA carrageenan, and a lambda carrageenan, are known by the above-mentioned carrageenan, the kappa and IOTA carrageenan which have gelation ability in this invention can be used for it. As a gelation adjuvant of this gelling agent carrageenan, about a kappa carrageenan, one sort of potassium ion, ammonium ion, and calcium ion or two sorts or more can be mentioned, and calcium ion can be mentioned about an IOTA carrageenan.
By the way, the concentration of the immersion fluid at the time of molding of the hard capsule for this invention physic (manufacture), i.e., a basis aqueous solution, contains the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical, and contains 0.1 - 0.5 % of the weight, and a gelation adjuvant for a gelling agent in 0.01 - 0.50% of the weight of the range five to 25% of the weight, respectively. At less than 5 % of the weight, if it is difficult to make the capsule coat of sufficient thickness form and the concentration of the cellulose ether replaced by the alkyl group concerned and the hydroxyalkyl radical, or the hydroxyalkyl radical exceeds 25 % of the weight, the jelly viscosity of a basis will become high and it will become difficult to cast [of the uniform capsule coat by dip coating] the concentration of the cellulose ether replaced by the alkyl group and hydroxyalkyl radical, or hydroxyalkyl radical in a basis aqueous solution. Therefore, especially the desirable concentration of the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical is 13 - 17 % of the weight.
If it slips down from a pin, without on the other hand the basis aqueous solution with which the concentration of the carrageenan as a gelling agent adhered to the molding pin at less than 0.1 % of the weight at the time of immersion molding gelling and 0.5 % of the weight is exceeded conversely, it will become easy to generate a gelation film in an immersion fluid vessel-wall side, and like the above-mentioned case, the jelly viscosity of a basis becomes high and molding of the uniform capsule coat by dip coating not only becomes difficult, but will

cause trouble at the time of capsule coat molding. Therefore, as optimum density of the gelling agent concerned, it is 0.15 – 0.30 % of the weight.
Furthermore, the use which crosses said under range and a range also about the concentration of said gelation adjuvant produces the case of a gelling agent, and same un-arranging. Therefore, as optimum density of this gelation adjuvant, it is 0.05 – 0.20 % of the weight.
In this invention, it does not bar blending suitably coloring agents, such as coloring matter and a pigment, opaquer, or perfume if needed in said basis like the well-known hard capsule for physic.
The hard capsule for this invention physic is manufactured according to the usual immersion casting method like a well-known gelatin hard capsule. That is, if it requires for the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical, a gelling agent and a gelation adjuvant, and a pan, a coloring agent, opaquer, perfume, etc. will be blended suitably, a basis aqueous solution will be adjusted, an immersion molding pin is immersed in this aqueous solution, and a hard capsule coat is obtained according to a conventional method below. At this time, the temperature of this basis aqueous solution, i.e., immersion fluid, is good to adjust to 50-52 degrees C. If the temperature of immersion fluid separates from said range, the jelly viscosity of this immersion fluid will change delicately, adhesion of immersion fluid at the molding pin at the time of immersion molding is not performed good, but it becomes difficult to obtain a uniform capsule coat as a result.
Henceforth, it is completely the same as the case of manufacture of the well-known ZERATEN hard capsule by dip coating that the coat from raising of the immersion molding pin from immersion fluid, desiccation, and a molding pin strips off (sampling), and the hard capsule of a predetermined size is obtained through production processes, such as decision. However, the case of this invention capsule takes long duration a little to the gelation duration of the basis immersion fluid in an immersion molding pin outside surface with 30 – 60 seconds to being 4 – 7 seconds in the case of a gelatin basis.
[Function]
Since this invention has the feature which was mentioned above, gelation of a basis is attained without requiring special heating, and it can form a flexible capsule coat also by the low water daily dose.
[Example]
This invention is explained in full detail still more concretely according to an example below.
Example 1 18.4g (gelation adjuvant concentration: 0.08 % of the weight) of potassium chloride is added into [purified water 19.55**] about 70 degrees C, and it dissolves, kappa carrageenan 39.1g (gelling-agent concentration: 0.17 % of the weight) is added further, and it dissolves, agitating these.
Next, it dissolves lowering this solution temperature to 50 degrees C, and agitating the hydroxypropyl methylcellulose, after supplying agitating hydroxypropyl-methylcellulose 3.45kg (cellulosic concentration: 15 % of the weight) to this solution and making it distribute in warm water, and after that, it puts for 7 hours and degassing is carried out.
Thus, the adjusted immersion fluid (basis aqueous solution) is taught to the well-known capsule manufacturing installation by dip coating, and the hard capsule of size No. 2 is obtained from a conventional method, holding the temperature of said immersion fluid at 50-52 degrees C.
Trial -1 (evaluation to the crack of an empty capsule)
About this invention hard capsule and the gelatin hard capsule as contrast which were obtained in said example, it was left for four days under the conditions of 12%RH, respectively, and the content moisture in a coat was reduced. Moreover, after drying at 105 degrees C about this sample for 2 hours, respectively and, making the content moisture in a coat 0% on the other hand, the crack condition was observed for both the sample capsule by the falling weight test method (49.7g weight is dropped from a height of 20cm), and the acupressure examining method.
Although the result is shown in the 1st table, it turns out that the hard capsule concerning

this invention is a pile thing clearly at a crack compared with a gelatin hard capsule.

第　1　表

カプセル	落錘試験		指圧試験	
	50個中の割れ個数	カプセル水分	10個中の割れ個数	カプセル水分
本発明品	0	1.1%	0	0%
対照品	46	8.8%	10	0%

Trial −2 (evaluation to the equilibrium moisture of a coat)
About the hard capsule and said contrast capsule of this invention obtained in the example, it was left for ten days under the condition with a humidity [of 43%RH], and a temperature of 25 degrees C, and after checking having reached at the balance, capsule moisture was measured by the loss−on−drying method, and the equilibrium moisture of a coat was investigated, respectively.
Although the result is shown in the 2nd table, the hard capsule of this invention has clearly low equilibrium moisture compared with a gelatin hard capsule, and it turns out that it is a low content moisture capsule.

第　2　表

カプセル	平衡水分
本発明品	4.3%
対照品	13.9%

Trial −3 (evaluation to the clarity and color of solution of an empty capsule)
About this invention hard capsule obtained in the example, and said contrast capsule, the clarity−and−color−of−solution trial using the purified water warmed at 37**1 degree C was performed on the standard conditions of a Japanese pharmacopoeia convention.
Although the result is shown in the 3rd table, a clarity and color of solution is completed within 10 minutes of the method convention of a station, and the hard capsule of this invention does not cause use top trouble, although a clarity and color of solution becomes late from a contrast capsule.

第　3　表

カプセル	溶解時間	
	平均	最小～最大
本発明品	8′16″	7′27″～9′45″
対照品	3′53″	3′26″～4′45″

(供試カプセル数：5)

Trial −4 (evaluation to collapsibility)
About this invention capsule obtained in the example, and said contrast capsule, it was filled up with corn starch, respectively and the disintegration test using the 1st liquid warmed at 37**1 degree C on the standard conditions of a Japanese pharmacopoeia convention was performed.
a result −− the 4th table −1 −− and −− said −− although this invention hard capsule became a little slow [decay] from the contrast capsule as shown in −2, it was checked that it is the hard capsule which all the contents flow out completely and it can fully use practically within 3 − 5 minutes.

第 4 表 － 1

カプセル	カプセル開口時間	
	平均	最小～最大
本発明品	2′43″	1′47″～4′14″
対照品	1′02″	0′57″～1′08″

（供試カプセル数：6）

第 4 表 － 2

カプセル	内容物流出完了時間	
	平均	最小～最大
本発明品	3′45″	2′50″～4′55″
対照品	2′03″	1′58″～2′15″

（供試カプセル数：6）

[Effect of the Invention]
Since the hard capsule for this invention physic makes main bases the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical as above-mentioned, it enjoys the property of the coat cast with this cellulosic as a feature of a hard capsule as it is. That is, according to this invention, the hard capsule of (1) low moisture content can be obtained, the hard capsule for physic which was further excellent also in the mechanical strength of the coat is offered, and the thing of it can be carried out.
(2) Since the equilibrium moisture in a coat is low, it can be filled up in the hard capsule concerned as it is also to the drugs which are easy to receive a bad influence with moisture, and capsule-izing is easy.
(3) A capsule coat does not insolubilize by the reaction with an aldehyde group or a carbonyl group.
(4) Without requiring special equipment and a special activity, since a gelling agent and a gelation adjuvant are used as an accessory constituent of a basis, the hard capsule manufacturing installation by well-known dip coating can be used as it is, and the hard capsule concerned can be offered cheaply.

[Translation done.]

* NOTICES *

TECHNICAL FIELD

[Industrial Application]
This invention relates to the new hard capsule for physic, the hard capsule of the low content moisture content which does not use gelatin especially well-known to a basis, the hard capsule for physic that made the water-soluble cellulosic the basis in more detail, and its manufacture method.

[Translation done.]

* NOTICES *

PRIOR ART

[Description of the Prior Art]

As everyone knows, the hard capsule for physic usually makes gelatin a basis, and is cast by this from plasticizers, such as a glycerol or a sorbitol, and the coat constituent with which addition combination of opaquer, a color, or the pigment was suitably carried out when requiring further. And this thing usually holds about 10 - 15% of the weight of moisture in this capsule coat.

If the content moisture in a capsule coat becomes 10 or less % of the weight, the plasticity of a coat will be lost, the shock resistance at the time of restoration of the drugs into the capsule concerned is spoiled remarkably, and it stops being equal to use. Moreover, if the empty or drugs restoration back is not asked but the content moisture content in a coat falls also at the time of conservation of this capsule, this coat contracts and it cannot avoid that fitting of a cap and the body becomes loose with time. Therefore, it is indispensable to make fixed moisture hold in the coat by the well-known gelatin hard capsule to apply as above-mentioned.

However, it decomposes and this gelatin hard capsule has caused [the fall of the potency of a chief remedy, deterioration, discoloration, and] un-arranging, such as insolubilization of a capsule coat, further, when the drugs with which the interior was filled up for the moisture in said coat tend to receive hydrolysis, or when two or more sorts of drugs with an interaction are contained.

Various amelioration and a proposal are made about the hard capsule for physic until now that such a defect should be canceled. For example, the water-soluble cellulose ether with which some or all of a hydroxyl group of a cellulose was replaced by the alkyl group or the hydroxy group is used as a basis, a molding pin is immersed in this water-soluble immersion fluid, and the manufacturing method of the hard capsule which forms a coat is indicated by JP,47-4310,B. Moreover, poly vinyl alcohol (PVA) is blended with said water-soluble cellulose ether, and it is indicated by JP,61-100519,A and the 62-266060 official report about the method of obtaining a hard capsule from this water-soluble immersion fluid.

[Translation done.]

* NOTICES *

EFFECT OF THE INVENTION

[Effect of the Invention]
Since the hard capsule for this invention physic makes main bases the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical as above-mentioned, it enjoys the property of the coat cast with this cellulosic as a feature of a hard capsule as it is. That is, according to this invention, the hard capsule of (1) low moisture content can be obtained, the hard capsule for physic which was further excellent also in the mechanical strength of the coat is offered, and the thing of it can be carried out.
(2) Since the equilibrium moisture in a coat is low, it can be filled up in the hard capsule concerned as it is also to the drugs which are easy to receive a bad influence with moisture, and capsule-izing is easy.
(3) A capsule coat does not insolubilize by the reaction with an aldehyde group or a carbonyl group.
(4) Without requiring special equipment and a special activity, since a gelling agent and a gelation adjuvant are used as an accessory constituent of a basis, the hard capsule manufacturing installation by well-known dip coating can be used as it is, and the hard capsule concerned can be offered cheaply.

[Translation done.]

* NOTICES *

TECHNICAL PROBLEM

[Problem(s) to be Solved by the Invention]
However, without said basis immersion fluid carrying out gelation solidification, if the heating is not enough since the coat adhering to the pin for molding or this pin itself is heated, gelation molding is carried out and it is manufactured, after the pin for molding is immersed in the basis immersion fluid of an aqueous solution cellulosic, immersion fluid slips down and these capsules for physic cannot obtain the capsule coat which may be satisfied practically from the pin for molding. Moreover, if heating temperature is too high, it will produce un-arranging -- a wrinkle tends to go into the coat at the time of gelation. Especially in the case of the latter, in case immersion gelation of the water-soluble cellulosic adhering to the pin for molding is carried out by underwater [hot], molding begins to melt underwater slightly, and it is [this] a sake. It is difficult it not only to become difficult to obtain a uniform coat, but for there to be a thing of molding, i.e., a capsule coat, for which a crack is generated plentifully from the pin for desiccation backward molding, even if it faces stripping off, and to obtain the hard capsule for physic of low moisture content practical anyway, since that jelly strength of this thing is small. furthermore, equipment and actuation special to enforcing these capsule manufacturing methods -- needing -- the immersion from the usual gelatin basis -- molding -- the most general well-known capsule manufacturing installation cannot be used as it is.
It is thought out in the above conditions and is going to improve the difficulty of the hard capsule which consists of a water-soluble above-mentioned cellulosic, and un-arranging, and the equilibrium moisture in a capsule coat is low, and does not embrittle under a low humidity condition, but this invention uses the crack after the drugs restoration by moisture, deterioration, etc. as a prevention plug.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

MEANS

[The means for solving a technical problem]
Gelation under a room temperature is enabled by adding and blending a gelling agent and a gelation adjuvant with this by making into a basis the cellulose ether with which this invention was replaced by the alkyl group and the hydroxyalkyl radical, and the basis was replaced by the hydroxyalkyl radical. Therefore, let the hard capsule for physic containing the cellulose ether, gelling agent, and gelation adjuvant by which this invention was replaced by the alkyl group and the hydroxyalkyl radical, and the basis was replaced by the hydroxyalkyl radical, and its manufacture method be the summary.
As cellulose ether replaced by the hydroxyalkyl radical, although the alkyl group used in this invention and a hydroxyalkyl radical, and a basis can mention the hydroxypropyl methylcellulose or hydroxypropylcellulose, they are the optimal in this in the point of the mechanical strength under a hydroxypropyl-methylcellulose coat moldability and low-water-flow part.
On the other hand, although a carrageenan, a tamarind seed polysaccharide, pectin, curdlan, gelatin, a furcellaran, an agar, etc. can be illustrated as an usable gelling agent in this invention, since it becomes usable by addition with a carrageenan little from the gelation nature which whose gel strength was high and was moreover excellent under coexistence with specific ion being shown, it is especially suitable. In addition, although three sorts, a kappa carrageenan, an IOTA carrageenan, and a lambda carrageenan, are known by the above-mentioned carrageenan, the kappa and IOTA carrageenan which have gelation ability in this invention can be used for it. As a gelation adjuvant of this gelling agent carrageenan, about a kappa carrageenan, one sort of potassium ion, ammonium ion, and calcium ion or two sorts or more can be mentioned, and calcium ion can be mentioned about an IOTA carrageenan.
By the way, the concentration of the immersion fluid at the time of molding of the hard capsule for this invention physic (manufacture), i.e., a basis aqueous solution, contains the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical, and contains 0.1 - 0.5 % of the weight, and a gelation adjuvant for a gelling agent in 0.01 - 0.50% of the weight of the range five to 25% of the weight, respectively. At less than 5 % of the weight, if it is difficult to make the capsule coat of sufficient thickness form and the concentration of the cellulose ether replaced by the alkyl group concerned and the hydroxyalkyl radical, or the hydroxyalkyl radical exceeds 25 % of the weight, the jelly viscosity of a basis will become high and it will become difficult to cast [of the uniform capsule coat by dip coating] the concentration of the cellulose ether replaced by the alkyl group and hydroxyalkyl radical, or hydroxyalkyl radical in a basis aqueous solution. Therefore, especially the desirable concentration of the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical is 13 - 17 % of the weight.
If it slips down from a pin, without on the other hand the basis aqueous solution with which the concentration of the carrageenan as a gelling agent adhered to the molding pin at less than 0.1 % of the weight at the time of immersion molding gelling and 0.5 % of the weight is exceeded conversely, it will become easy to generate a gelation film in an immersion fluid vessel-wall side, and like the above-mentioned case, the jelly viscosity of a basis becomes high and molding of the uniform capsule coat by dip coating not only becomes difficult, but will cause trouble at the time of capsule coat molding. Therefore, as optimum density of the

gelling agent concerned, it is 0.15 − 0.30 % of the weight.
Furthermore, the use which crosses said under range and a range also about the concentration of said gelation adjuvant produces the case of a gelling agent, and same un-arranging. Therefore, as optimum density of this gelation adjuvant, it is 0.05 − 0.20 % of the weight.
In this invention, it does not bar blending suitably coloring agents, such as coloring matter and a pigment, opaquer, or perfume if needed in said basis like the well-known hard capsule for physic.
The hard capsule for this invention physic is manufactured according to the usual immersion casting method like a well-known gelatin hard capsule. That is, if it requires for the cellulose ether replaced by the alkyl group and the hydroxyalkyl radical, or the hydroxyalkyl radical, a gelling agent and a gelation adjuvant, and a pan, a coloring agent, opaquer, perfume, etc. will be blended suitably, a basis aqueous solution will be adjusted, an immersion molding pin is immersed in this aqueous solution, and a hard capsule coat is obtained according to a conventional method below. At this time, the temperature of this basis aqueous solution, i.e., immersion fluid, is good to adjust to 50-52 degrees C. If the temperature of immersion fluid separates from said range, the jelly viscosity of this immersion fluid will change delicately, adhesion of immersion fluid at the molding pin at the time of immersion molding is not performed good, but it becomes difficult to obtain a uniform capsule coat as a result. Henceforth, it is completely the same as the case of manufacture of the well-known ZERATEN hard capsule by dip coating that the coat from raising of the immersion molding pin from immersion fluid, desiccation, and a molding pin strips off (sampling), and the hard capsule of a predetermined size is obtained through production processes, such as decision. However, the case of this invention capsule takes long duration a little to the gelation duration of the basis immersion fluid in an immersion molding pin outside surface with 30 − 60 seconds to being 4 − 7 seconds in the case of a gelatin basis.

[Translation done.]

* NOTICES *

1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

OPERATION

[Function]
Since this invention has the feature which was mentioned above, gelation of a basis is attained without requiring special heating, and it can form a flexible capsule coat also by the low water daily dose.

[Translation done.]

* NOTICES *

EXAMPLE

[Example]
This invention is explained in full detail still more concretely according to an example below.
Example 1 18.4g (gelation adjuvant concentration: 0.08 % of the weight) of potassium chloride is added into [purified water 19.55**] about 70 degrees C, and it dissolves, kappa carrageenan 39.1g (gelling-agent concentration: 0.17 % of the weight) is added further, and it dissolves, agitating these.
Next, it dissolves lowering this solution temperature to 50 degrees C, and agitating the hydroxypropyl methylcellulose, after supplying agitating hydroxypropyl-methylcellulose 3.45kg (cellulosic concentration: 15 % of the weight) to this solution and making it distribute in warm water, and after that, it puts for 7 hours and degassing is carried out.
Thus, the adjusted immersion fluid (basis aqueous solution) is taught to the well-known capsule manufacturing installation by dip coating, and the hard capsule of size No. 2 is obtained from a conventional method, holding the temperature of said immersion fluid at 50-52 degrees C.
Trial -1 (evaluation to the crack of an empty capsule)
About this invention hard capsule and the gelatin hard capsule as contrast which were obtained in said example, it was left for four days under the conditions of 12%RH, respectively, and the content moisture in a coat was reduced. Moreover, after drying at 105 degrees C about this sample for 2 hours, respectively and, making the content moisture in a coat 0% on the other hand, the crack condition was observed for both the sample capsule by the falling weight test method (49.7g weight is dropped from a height of 20cm), and the acupressure examining method.
Although the result is shown in the 1st table, it turns out that the hard capsule concerning this invention is a pile thing clearly at a crack compared with a gelatin hard capsule.

第 1 表

カプセル	落錘試験		指圧試験	
	50個中の割れ個数	カプセル水分	10個中の割れ個数	カプセル水分
本発明品	0	1.1%	0	0%
対照品	46	8.8%	10	0%

Trial -2 (evaluation to the equilibrium moisture of a coat)
About the hard capsule and said contrast capsule of this invention obtained in the example, it was left for ten days under the condition with a humidity [of 43%RH], and a temperature of 25 degrees C, and after checking having reached at the balance, capsule moisture was measured by the loss-on-drying method, and the equilibrium moisture of a coat was investigated, respectively.
Although the result is shown in the 2nd table, the hard capsule of this invention has clearly low equilibrium moisture compared with a gelatin hard capsule, and it turns out that it is a low content moisture capsule.

第　　2　　表

カプセル	平衡水分
本発明品	4.3%
対照品	13.9%

Trial −3 (evaluation to the clarity and color of solution of an empty capsule)
About this invention hard capsule obtained in the example, and said contrast capsule, the clarity−and−color−of−solution trial using the purified water warmed at 37**1 degree C was performed on the standard conditions of a Japanese pharmacopoeia convention.
Although the result is shown in the 3rd table, a clarity and color of solution is completed within 10 minutes of the method convention of a station, and the hard capsule of this invention does not cause use top trouble, although a clarity and color of solution becomes late from a contrast capsule.

第　　3　　表

カプセル	溶解時間	
	平均	最小～最大
本発明品	8′16″	7′27″～9′45″
対照品	3′53″	3′26″～4′45″

(供試カプセル数：5)

Trial −4 (evaluation to collapsibility)
About this invention capsule obtained in the example, and said contrast capsule, it was filled up with corn starch, respectively and the disintegration test using the 1st liquid warmed at 37**1 degree C on the standard conditions of a Japanese pharmacopoeia convention was performed.
a result −− the 4th table −1 −− and −− said −− although this invention hard capsule became a little slow [decay] from the contrast capsule as shown in −2, it was checked that it is the hard capsule which all the contents flow out completely and it can fully use practically within 3 − 5 minutes.

第　4　表　−　1

カプセル	カプセル開口時間	
	平均	最小～最大
本発明品	2′43″	1′47″～4′14″
対照品	1′02″	0′57″～1′08″

(供試カプセル数：6)

第　4　表　−　2

カプセル	内容物流出完了時間	
	平均	最小～最大
本発明品	3′45″	2′50″～4′55″
対照品	2′03″	1′58″～2′15″

(供試カプセル数：6)